REMARKS/ARGUMENTS

Reconsideration of this patent application is respectfully requested in view of the foregoing amendments, and the following remarks. Claims 1-22 and 25-34 are in the application. Claims 23, 24 and 35 have been canceled. Claims 1, 13, 16, 18, 19, 22, 31, 32 and 34 have been amended. The specification has been amended. No new matter has been added.

The Examiner objected to the specification for improper designation of trademarks. Applicant has amended the specification and claim 22 to indicate the trademarked names in capital letters and a trademark symbol. The Examiner objected to the Abstract for being too long. Applicant submits herewith a new Abstract.

The Examiner rejected claims 1-35 under 35 USC §112, second paragraph, for being indefinite. Applicant has amended claims 1, 13, 16, 18, 19, 22, 31, 32 and 34 according to the Examiner's suggestions, and to further clarify the invention.

The Examiner rejected claims 1-35 under 35 USC §112, first

paragraph, for being non-enabled. Applicant respectfully traverses.

The major concern raised by the examiner is that, while in the example, the invention show how the patent would work for normal B-cells and mature B-cell neoplasias, one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation in other disease-types.

As mentioned in the text of the patent and more specifically in the background section (6th paragraph), it is clearly stated that "in the last decade many different reports have been published which show that neoplastic cells from a great majority of patients suffering from haematological malignancies display aberrant patterns of antigen expression as detected through the use of several triple and quadruple combinations of monoclonal antibodies analyzed by flow cytometry (Reviewed in Vidriales et al, Best Clin Res Pract, 2003; 16: 599-612)". In addition, "based on these abnormalities, several disease-type specific panels of three and four color combinations of monoclonal antibody reagents have been proposed for the systematic identification of leukemic cells expressing aberrant phenotypes, in virtually every patient

with precursor B-Acute lymphoblastic leukemia (ALL; Lucio et al, Leukemia, 2001; 15: 1185-1192), T-ALL (porwit-MacDonald, Leukemia, 2000; 14: 816-825), acute myeloblastic leukemia (AML; San Miguel et al, Blood, 2001; 98: 1746-1751), B-cell chronic lymphocytic leukemia (Rawstron et al, Blood 2001; 98: 29-35) and other B-cell chronic lymphoproliferative disorders (Sanchez et al, Leukemia, 2002; 16: 1460-1469), among other diseases". This means that any of these panels could be used just by adding in each panel of combinations of monoclonal antibodies at least three of the monoclonal antibodies in the panel in common in every combination in the panel.

As an illustrating example, the inventor selected as three common reagents for every combination of monoclonal antibodies in the B-cell chronic lymphocytic leukemia panel, CD45, CD19 and CD5. These as well as the other reagents in the selected panel can be easily found in the literature (see cited references by Rawstron et al and Sanchez et al, plus Barrena et al, Leukemia, 2005) as useful for detecting aberrant phenotypes in B-cell chronic lymphoproliferative disorders, and they should be considered as prior art. The combination of reagents selected in the example is just for illustrating purposes and should not

limit the areas of application of the patent. Therefore, based on what is described above, the inventors could build panels of combinations of monoclonal antibodies containing at least three monoclonal antibodies in common for the detection of aberrant neoplastic cells in other haematological malignancies without further need for experimentation and just based on information from the literature. What is unique and important here is that all combinations of monoclonal antibodies in a panel contain at least three reagents in common to allow appropriate merge of the data files.

As mentioned in the text of the patent application, the combination of three or more monoclonal antibodies common to all combinations of monoclonal antibodies in a panel, should be able to identify the neoplastic cells in a specific disease-type, as described for instance in the references cited in the 6th paragraph of the background section and above and in the other references mentioned in the text of the patent for the identification and enumeration of normal cells in a body fluid (Loken and Terstappen, US Patent 5,047,321; Terstappen and Chen, US Patent 6,287,791; Loken and Sha, US Patent, 5,137,809). Based on this prior information and the fact that it is not necessary

to show working examples for every possible embodiment, Applicant submits that there is sufficient teachings in the specification that would suggest to the skilled person how to do it.

The Examiner rejected claims 1, 3, 6-13, 15-17, 19, 20, 23-25, 34 and 35 under 35 USC 103 as being unpatentable over Nagler et al. Claims 2, 4, 5, 18, 22, 26, 27 and 30-33 are rejected as being unpatentable over Nagler et al. in view of Ward. Claims 2, 14 and 26-33 are rejected as being unpatentable over Nagler et al. in view of Orfao De Matos et al. Applicant respectfully traverses.

Certainly Nagler et al., as many others, have described multiple aberrant phenotypes in neoplastic haematopoieic cells. For this purpose, strategies based on the use of variable panels of monoclonal antibody combinations for the identification of such aberrant phenotypes have been employed which are expert-based. However, they fail to teach the use of three or more common reagents in every combination that would provide consistency for the information measured in the different aliquots of a sample stained each with a different combination of monoclonal antibodies that is essential for the strategy proposed

in the current patent application.

In addition, in Nagler et al. an expert is used to perform data interpretation which, as mentioned in the text of the present patent application, is common practice "in all approaches described so far for the identification of aberrant phenotypes expressed by neoplastic cells". The former approaches fail to teach a way of directly comparing, in a single data file, the information measured for the neoplastic cells with that collected through the use of the same combinations of monoclonal antibodies to stain a normal/reactive sample. In fact, they show comparisons of printed dot plots in two-dimensional spaces. In contrast, they fail in teaching to merge data from different normal/reactive and neoplastic samples measured by flow cytometry into a single data file (see for instance, the text of claim 1, step d) of the current patent application) to allow for direct comparison between normal and neoplastic events in a multidimensional space as large as that formed by all parameters evaluated (two light scatter and 21 fluorescence emissions corresponding to different non-overlapping monoclonal antibodies, in the case of the panel used by Nagler et al); analysis of measured flow cytometric data cannot be done in an objective way

in the head of an expert just by looking at 2 or a maximum of 3-dimensions each time (see Orfao et al, The Hematology Journal, 2006, attached to this letter). This limitation is even overemphasized by the fact that the PAINT-A-GATE software program used by Nagler et al. cannot handle simultaneously more that 7 parameters and is limited to a maximum of 3-dimensional data representation, the possibility of identifying cell populations with regions being restricted to 2-dimensional plots.

In addition, as mentioned in the text of the current patent application "if data files containing information on the light scatter and fluorescence characteristics of cells from multiple different samples are merged" (or compared) "and they have been acquired under different conditions...or at different times..., the relative position is adjusted automatically by software operations based on the relative changes observed in the position of the populations of internal reference microparticles measured simultaneously with the cells" (paragraph 5 at the bottom of the section describing the invention of the current patent application). In the case of Nagler et al, this later concern would apply since samples were collected at different times

(e.g.: prior to BMT and 3-4 months after BMT) and no correction of data was used. Correction increases comparability and objectivity (and therefore it also increases the sensitivity of the assay).

As with Nagler et al., Ward et al. also fails to teach the use of three or more common reagents in every combination that would provide consistency for the information measured in the different aliquots of a sample each stained with a different combination of monoclonal antibodies and is essential for the strategy proposed in the current patent application. In addition, Ward et al. teaches the use of internal reference microparticles for absolute counting, which means counting the number of cells per unit of volume of the fluid in which they are contained. However, the addition of internal reference particles as described in the application has a completely different goal. Accordingly, as mentioned in the text of the current patent application "if data files containing information on the light scatter and fluorescence characteristics of cells from multiple different samples are merged" (or compared) "and they have been acquired under different conditions...or at different times..., the relative position (of the measured cells in a data file) is

adjusted automatically by software operations based on the relative changes observed in the position of the populations of internal reference microparticles measured simultaneously with the cells" (paragraph 5 at the bottom of the section describing the invention). The operations to be performed are further described in the text and they can be compared with those described by Ward et al., confirming that they are used for completely different purposes. The use of these internal reference particles for adjusting the relative position of the populations of cellular events measured according to pre-established standards is clearly mentioned in claim 27 and the related claim 26 of the current patent application. This is clearly expressed also in the 4th paragraph of the example described in the text of the present patent application. What is claimed in the text of the patent application is that these internal reference microparticles used as internal reference standards, which were used to correct for the position of cellular events measured from a sample in a merged data file, can be added in known numbers (see claim 33). In such a case, apart from being used to correct for the position of cellular events in a data file, these particles could also be used to derive absolute cell counts (and not only to correct for the position of

cellular events in a file).

As with Nagler et al, Orfao de Matos also fails to teach the use of three or more common reagents in every combination that would provide consistency for the information measured in the different aliquots of a sample stained each with a different combination of monoclonal antibodies, a step that is a key step essential for the strategy proposed in the current patent application. In addition, Orfao de Matos teaches the use of internal reference microparticles for controlling absolute cell counting by flow cytometry, which means controlling the counting of the number of cells per unit of volume of a fluid in which the cells are contained. However, the addition of internal reference particles as described in our patent has a completely different goal. Accordingly, as mentioned in the text of the current patent application "if data files containing information on the light scatter and fluorescence characteristics of cells from multiple different samples are merged" (or compared) "and they have been acquired under different conditions...or at different times..., the relative position (of the measured cells in a data file) is adjusted automatically by software operations based on the relative changes observed in the position of the populations

of internal reference microparticles measured simultaneously with the cells" (paragraph 5 at the bottom of the section describing the invention). The operations to be performed are further described in the text and they can be compared with those described by Ward et al., confirming that they are used for completely different purposes. The use of these internal reference particles for adjusting the relative position of the populations of cellular events measured according to pre-established standards is clearly mentioned in claim 27 and the related claim 26 of the current patent application. This is clearly expressed also in the 4th paragraph of the example described in the text of our current patent application. What is claimed in the text of our current patent application is that these internal reference microparticles used as internal reference standards, which were used to corrected for the position of cellular events measured from a sample in a merged data file, can be added in known numbers (see claim 33). In such a case, apart from being used to correct for the position of cellular events in a data file, these particles could also be used to derive absolute cell counts (and not only to correct for the position of cellular events in a file).

Combining Nagler with Ward and/or Orfao De Matos would not lead to the present invention because none of the references teaches or suggests the use of three or more common reagents in every combination that would provide consistency for the information measured in the different aliquots of a sample stained with a different combination of monoclonal antibodies.

Accordingly, Applicant submits that the amended claims are patentable over the cited references, taken either singly or in combination. Early allowance is respectfully requested.

Applicant also submits herewith a Supplemental Information Disclosure Statement, together with a check in the amount of $180.00 to cover fee for filing an Information Disclosure Statement after the issuance of an Office Action.

Respectfully submitted,
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Enclosures:
Abstract
Supplemental Information Disclosure Statement
PTO Form 1449 with one (1) reference
Check in the amount of $180.00

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: MAIL STOP AMENDMENT, Commissioner for Patents, Alexandria, VA, on August 6, 2007.

Kelly Espitia